REMARKS

Claim Objections

In Paragraph 2 of the office action, the examiner has objected to claims 17 and 18 pursuant to 37 CFR 1.75 (c) as being in improper dependent form for failing to further limit the subject matter of the previous claim. The examiner notes that claims 17 and 18 include additional species of body fluids not recited in claim 1. In response to this objection the applicant has amended claims 17 and 18 to recite only the body fluids recited in claim 1 and has added claims 19 and 20 dependent on claims 17 and 18 respectively reciting the additional body fluids set forth in the original claims 17 and 18.

Claim Rejections - 35 U.S.C. §112 - Second Paragraph

In paragraphs 3 and 4 of the office action the examiner has rejected claims 1 through 18 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as his invention. It is stated that claim 1 is rendered indefinite by the recitation of the phrase "such as" because it is unclear whether the limitations following the phrase are part of the claimed invention. In response the applicant has amended claim 1

to remove the phrase "such as" and to make the claim definite as to the body fluids claimed to be the subject matter of the invention.

Claims 17 and 18 are also rejected for lacking an active method step relating the comparison of the lipid associated sialoprotein levels with the diagnosis of cancer.

The rejection of claims 17 and 18 for lacking an active method step relating the comparison of lipid associated sialoprotein levels with the diagnosis of cancer is traversed. The invention pertains to a method of measuring lipid associated sialoprotein levels (LSP) in patients who have cancer or are known to have a brain tumor. The method of the invention can also be used to distinguish patients with malignant primary and metastatic brain tumors by measuring the increase in LSP. The invention is also used to determine a response to treatment and to monitor radiation and chemotherapy in patients known to have cancer. The method of the invention is also used to identify early metastasis of cancer in other parts of the body which enter the spinal fluid and travel to the brain even before an MRI will locate a tumor in the brain. Thus it is also an objective of the invention that the test be used with a patient known to have cancer but in remission due to therapy should a malignant tumor develop in other parts of the body including the brain.

The active method step in claim 17 as with other tumor markers is the comparison of the levels of LSP in a particular subject with levels previously determined from other subjects known to have cancer. Similarly the active method step of claim 18 is the comparison of levels of LSP of a human subject known to have cancer and being treated therefor with levels previously determined for that same subject.

Claim 17 and 18 have been amended to make it clear that the claims relate to the use of the method of claim 1 to obtain all of the LSP values being compared.

Claim Rejections - 35 U.S. C. §112 (First Paragraph)

In paragraphs 5 through 7 the examiner rejects claims 1 through 18 under 35 U.S.C. 112, first paragraph for failing to enable a person skilled in the art to which it pertains to practice the invention commensurate with the scope of the claims. In support of this position the examiner states in paragraph 6 that other sialoprotein species such as free sialoprotein or protein bound sialoprotein would be present in the upper phase along with the lipid associated sialoprotein that would be effectively separated from said lipid component in the lower organic phase with the alkyl hydrocarbons. The examiner concludes that the

specification does not provide for the removal of the non-lipidated hydrocarbons prior to the lipidated hydrocarbons or vice versa. The examiner further concludes that both lipidated and non-lipidated sialoproteins will be present in the upper or aqueous layer and therefor that the specification is enabling for a method of extracting sialoproteins from cerebral spinal fluid, urine, saliva and sputum but not for a method of extracting only lipid sialoproteins.

The foregoing rejection is traversed. The examiner's conclusion is based on the analysis that there are only two phases, an upper phase and a lower phase. In fact, there are three phases. The bulk of the free sialoprotein or protein bound sialoprotein will be at the bottom of the upper phase forming a thick layer of interphase between the upper phase and the lower phase. This is the result of two new steps introduced in the invention over the prior art. The first is centrifugation at 6,000 rpm which brings down all of the debris and compacts it in the intermediate layer. The second new step introduced in the invention is the washing of the upper phase with a saline solution and centrifuging again in order to clean all unseparated free sialoproteins and other contaminants from the upper phase. Thus the upper phase will be free of free sialoprotein and protein bound sialoprotein and will

contain substantially only the lipid associated sialoprotein. The applicant has amended Page 9 of the specification to correct a typographical error pertaining to the centrifugation speed. The speed of 6000 rpm rather than 1000 rpm was intended as evidenced by original claim 6.

In Paragraph 7 the examiner rejects claim 18 under 35 U.S.C. 112 first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make or use the invention. The examiner states that the specification provides no guidance on when to make said determination or the time intervals between such determinations. The applicant traverses this rejection. Claim 18 deals with the use of the invention with a patient known to have cancer. The invention can be used in a variety of scenarios. First there may be the patient who has had cancer but is believed to be in remission and the method of the invention is used periodically at intervals determined by the physician to determine if any cancer cells have migrated to the brain. In another case, a patient may experience headaches, blurred vision or the like. If a scan finds something then typically a biopsy would be done and if malignant, a regimentation of radiation therapy would begin. The test of the invention would be used at intervals, once again

determined by the physician, to monitor the therapy and to avoid periodic scans which are expensive and which can cost as much as $1,800 per scan. In these cases, a scan such as an MRI would typically detect a tumor in the first instance. What is claimed is that the test of the invention would be used to monitor treatment and to avoid the necessity of repetitive expensive scans.

In other situations there may be something shown by a scan leading to the requirement to determine whether or not the tumor is malignant or benign. The test of the invention may determine this and may confirm a following biopsy or obviate the need for a biopsy.

Claim Rejections - 35 U.S.C. §103

In Paragraphs 8 through 11 the examiner rejects all the claims based on 35 U.S.C.103(a) as being obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter of the invention pertains. In Paragraph 9 the examiner rejects claims 1 through 16 for obviousness as being unpatentable over ***Katopodis (US 5,045,453)*** in view of ***Gernez-Rieux et al (Pathologie et Biologie, 1963, Vol. 11, pp. 729-741)***. The examiner concedes that ***Katopodis et al*** do not teach a method of extracting sialoprotein from sputum. However, the examiner points

out that ***Gernez-Rieux*** teaches the determination of sialoprotein in the sputum of patients having chronic bronchitis and asthma as a measurement of disease state. This rejection is traversed.

The examiner is quite correct in the observation that ***Katopodis et al*** do not teach a method for extracting sialoprotein from sputum. The applicant rejects the examiner's conclusion that a man of ordinary skill in the art having before him the teaching of ***Katopodis et al*** and ***Gernez-Rieux*** would have used the method of the invention for the determination of sialoprotein in sputum of patients having cancer. ***Gernez-Rieux*** teaches the use of electrophoresis, chromatography and immuno-chemistry in analyzing bronchial fluids and teach the measurement of sugars in the bronchial expectorant such as fructose, sialic acid and glycosides. They do not teach the isolation and measurement of the complex of lipid sialoprotein as does the invention. A man of ordinary skill in the art would not be motivated to measure the lipid sialoprotein complex even if he had the teaching of ***Katopodis et al*** before him. The teaching of ***Gernez-Rieux*** have nothing whatsoever to do with the analysis of body fluids containing LSP.

In Paragraph 10 the examiner rejects claims 1 through 17 as being unpatentable over ***Katopodis et al*** in view of ***Bellahcene et al (British Journal of Haematology, 2000, Vol. 111, pp. 1118-1121)***.

The examiner points out that these claims are drawn in part to a method of diagnosing cancer in a human subject comprising the determination of the amount of sialoprotein in peritoneal fluid. The examiner points out that ***Katopodis et al*** teaches "the exact method" of claims 1 through 16 for extracting sialoprotein from serum and plasma although they do not teach a method of extracting sialoprotein from peritoneal fluid. The examiner relies on the teaching of ***Bellahcene et al*** for the detection of multiple myeloma comprising the detection of sialoprotein in an ascites sample. This rejection also is traversed. It is incorrect to state that ***Katopodis et al*** teaches "the exact method" of claims 1 through 16 for extracting sialoprotein from serum and plasma. There are several new and inventive steps such as recited above regarding the greatly increased centrifugal speed and the new step of washing the upper layer as previously discussed. Moreover, the analysis taught by ***Bellahcene*** utilizes cell culture and cytology, not chemistry, and certainly not the chemistry disclosed in the application. There would be no reason whatsoever for a chemist to look to ***Bellahcene*** for teaching which would aid in the chemistry necessary to extract, isolate and measure the LSP complex.

In Paragraph 11 claims 1 through 17 are rejected as being unpatentable over ***Katopodis***, in view of ***Figarella-Branger et al***

(Cancer Research, 1990, Vol 50, pp. 6364-6370) or Rao et al (Trans All-India Institute of Mental Health, 1969, Vol. 9, pp. 35-38). The examiner notes that claims 1 through 17 are drawn in part to a method of diagnosing cancer in a human subject comprising the determination of the amount of sialoprotein in cerebrospinal fluid. The examiner correctly notes that ***Katopodis et al*** do not teach a method of extracting sialoprotein from cerebrospinal fluid. It is, however, the examiner's position that ***Figarella-Branger et al*** teach the detection of medulloblastoma metastases by measuring highly sialylated isoforms of N-CAM protein in the cerebrospinal fluid of patients. The examiner points out that ***Rao*** teaches the detection of spinal tumors comprising the measurement of sialic acid in cerebrospinal fluid. As the examiner notes, ***Rao et al*** do not specifically teach that the sialic acid residue being detected are in the form of sialoprotein. This rejection is also traversed. ***Figarella-Branger et al*** is a study of the adhesiveness of brain tumors. They deal with neuro cell adhesion molecule isoforms (N-CAM) and HNK1 epitope by Western blotting and double immuno-fluorescence labeling. ***Figarella-Branger*** teach an analysis of tissue after a biopsy and thus are involved in the cytology of brain tumors and not the analysis of body fluids containing lipid sialoproteins as does the invention of this application. Nor is

the invention rendered obvious by ***Katopodis et al*** in view of Rao. Rao uses the method of ***Popodopoulos*** and ***Hess*** which was published in 1960. They teach the determination of glucose and fructose in spinal fluid as well as protein and free total neuraminic acid (sialic acid). The authors did not measure the LSP as a whole complex as extracted from cerebrospinal fluid. Moreover, the publication teaches that CSF protein increased only in the case of meningitis and spinal cord tumors. The applicant notes that Rao found brain tumors only 22% of the time suggesting that the process is not validated. Moreover, ***Rao*** deals with the separate components of LSP and not the LSP as an entire complex and fails to teach with respect to lipid bound sialoprotein. The teaching of ***Rao*** deals with patients having both psychiatric and neurological disorders and teaches that a significant increase of total and free sialic acid levels were noted in patients with TB, meningitis and spinal cord tumors. There is no indication that the authors were dealing in any way with the entire complex of lipid bound sialoprotein as does the invention nor that it would be useful at all with respect to measuring cancer levels in a human subject. Indeed in the teaching of ***Rao et al*** there is no distinction at all between benign and malignant tumors.

CONCLUSION

It is respectfully requested that the rejections based on 37 CFR 1.75 (c) and 35 U.S.C. §112 be withdrawn based on the amendment of the specification and claims and on the applicant's explanation of the chemistry of the invention. It is also requested that the rejections under 35 U.S.C. §103 be withdrawn based on applicant's analysis of the distinctions between the teachings of the prior art publications cited and the teaching of the invention. The applicant believes that the application as amended is now in condition for allowance.

Respectfully submitted,

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